Remarks/Arguments

Prior to this amendment, Claims 1, 3-5, and 45-48 were pending. By this amendment, Claim 1 has been amended and Claim 45 has been canceled without prejudice. The Applicant reserves the right to prosecute canceled subject matter in a continuation application. Following entry of this amendment, Claims 1, 3-5, and 46-48 will be pending.

First Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5, and 45-48 have been rejected for lack of enablement. The Examiner has asserted that undue experimentation would be required to practice the full scope of the claimed invention. The rejection is respectfully traversed.

The Examiner has stated that there are no animal models of psoriasis. Although the Applicant does not concede that the invention would not be applicable to any animal (other than a human) having a skin disease characterized by excessive proliferation of epidermal cells, in the interest of facilitating allowance, the Applicant has amended Claim 1 to recite "human" and canceled Claim 45.

The Examiner has asserted that the specification fails to teach an effective amount of an antibody to be administered. To the contrary, the instant specification teaches the properties of the antibodies to be administered, along with routes of administration, and discloses dosages and exemplifies the desired pharmacological effect. The Applicant respectfully draws the Examiner's attention to the specification, for example, at page 14, lines 13-25, where dosage guidelines and amounts are provided. The amounts are applicable for antibodies in general, and C225 in particular. The amounts are consistent with the dosages received by the clinical trial subject that had a complete response with respect to psoriasis (Example 2). The amounts are also consistent with dosages disclosed in Example 1. One of skill in the art would understand that a preferred dose achieves the maximal response, and would also be able to correlate dosages and desired responses by other means, such as measurement of EGFR-tyrosine kinase activity for determination of receptor saturation (Example 1). Such determinations are applicable to C225, as well as other anti-EGFR/HER1 antibodies.

The Applicant respectfully submits that an effective dose or dose intensity of an anti-EGFR antibody is either known to, or readily can be determined by, one of ordinary skill in the art, for this is a routine step in the clinical development of a drug. By way of example, preclinical and clinical trials, such as phase I clinical trials, are routinely conducted as part of the development of a drug, and serve to determine effective doses and dose intensities.

The enablement rejection is also based on the Examiner's assertion that the specification confines its teachings to administration of a specific anti-EGFR/HER1 antibody (C225) in combination with a chemotherapeutic agent to a cancer patient who suffered from psoriasis, and the further assertion that the specification does not make clear whether the improvement in psoriasis was due to C225 administration, or to the chemotherapeutic agent or combination of the two.

Applicant respectfully points out that the specification is not limited to a combination therapy. The specification discloses treatment of a hyperproliferative disease with an EGFR antibody or other EGFR antagonist (e.g., page 3, lines 10-15) and provides that the EGFR antagonists of the invention inhibit excess growth of cells associated with hyperproliferative disease when administered in an effective amount (e.g., page 14, lines 9-11). As already pointed out, the specification provides dosage guidelines and amounts (e.g., page 14, lines 13-25). The specification also discloses that such treatment can be combined with administration of a chemotherapeutic agent, radiation, or phytotherapy (e.g., page 3, lines 16-24; page 15, line 2 to page 19, line 9.). The Examples disclose a combination treatment using C225 with a chemotherapeutic agent because Applicant's invention was discovered in the context of a clinical trial for treatment of refractory colon cancer. The Applicant discovered that the improvement in psoriasis was peculiar to a patient whose treatment included administration of an anti-EGFR/HER1 antibody, as opposed to a standard regimen of chemotherapy alone. However, compliance with the enablement requirement does not turn on whether an example is disclosed. (MPEP § 2164.02) The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Here, even though the Examples describe

coadministration of an anti-EGFR/HER1 antibody with a therapeutic agent, the specification clearly sets forth how to use the anti-EGFR/HER1 antibody alone.

Applicant respectfully asserts that the Examiner has not made out a case of non-enablement with respect to the effectiveness of treatment with an anti-EGFR/HER1 antibody alone. To object on such grounds, the burden is on the Examiner to provide evidence or technical reasoning substantiating any belief that treatment with an anti-EGFR/HER1 antibody alone, as disclosed in the specification, would not provide the desired result, and this the Examiner has not done. (See, MPEP § 2164.04). Without a reason to doubt the truth of the statements made in the patent specification, the application must be considered enabling. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). Accordingly, Applicant respectfully asserts that this basis for an enablement rejection is improper.

With respect to any confusion as to the identity of certain chemotherapeutic agents, in combination treatments, any of the disclosed chemotherapeutic agents can be used.

In summary, the Applicant asserts that no undue experimentation is necessary to practice the claimed invention. The instant claims recite treatment of a human with an anti-EGFR/HER1 antibody such as C225, and the specification teaches administration of such an antibody in an amount effective to treat psoriasis. Accordingly, it is requested that the rejection be withdrawn.

Second Rejection Under 35 U.S.C. § 112, first paragraph

Claim 48 has been rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that is not enabled insofar as it recites using the C225 monoclonal antibody. The Examiner has indicated that a suitable deposit of the hybridoma producing C225 is required. The rejection is respectfully traversed.

The Applicant asserts that a deposit is not necessary even though Mab C225 is required to practice the claimed method because Mab C225 is known in the art and any required information or biological materials can routinely be obtained from publicly available material. MPEP § 2404.02. The specification discloses that C225 is a chimerized version of Mab 225 (see, e.g., Specification , page 11, lines 8-10). C225 is otherwise known in the art.

antibody is known in the art. For example, Cardiello, 1999, Clinical Cancer Research 5:909-916, discloses that C225 is an anti-EGFR human-mouse chimeric MAb 225 (Exhibit A; see, page 910, col. 1, lines 24-30, and col. 1, "Materials."). The specification further provides instruction as to the making of C225 (see, e.g., page 11, lines 15-17; page 8, line 26 to page 9, line 1). Amino acid and nucleic acid sequences for the murine Mab 225 heavy and light chains are disclosed in publications that are cited in the specification (*see, e.g.*, Wels et al., 1995, Int. J. Cancer 60:137 and WO 96/40210 (Goldstein et al.) Figs. 13 and 14). Only routine experimentation would be required to synthesize and express nucleic acids having the disclosed sequences with nucleic acids encoding heavy or light chain constant domains. Accordingly, it is requested that the enablement rejection be withdrawn.

Conclusion

It is believed that this amendment is fully responsive to the outstanding Office Action, and favorable action is respectfully requested. If a telephone conversation would further the prosecution of the present application, the Examiner is invited to contact the undersigned to resolve any issues that might remain.

Respectfully submitted,

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